PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	01 DEC 2004
Applicant's or agent's file reference C1102.70007	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/14996	12 May 2004 (12.05.2004)	13 May 2003 (13.05.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07H 21/02, 21/04; A01N 63/00, 65/00; C12N 5/00, 5/02; A01K 67/00, 67/033 and US Cl.: 536/23.1; 424/93.1; 435/325; 800/8

Applicant

THE REGENTS OF THE UNIVERSITY OF COLORADO

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/14996

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/14996

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 13-21 and 31-38	YES
	Claims 1-12, 22-30	NO
Inventive step (IS)	Claims 13-21, 31-38	YES
	Claims 1-12, 22-30	NO
Industrial applicability (IA)	Claims 1-12, 22-30	YES
	Claims 13-21, 31-38	NO

2. Citations and explanations:

The pathology in Down's Syndrome patients caused by the third copy of chromosome 21 is unclear. The art has shown that there does not appear to be a strong correlation between the genes expressed on chromosome 21 and some of the pathology seen in Downs Syndrome patients. This application appears to have three primary foci: 1) a method of detecting mitochondrial defect in a maternal sample of blood, a kit used for assessing mitochondrial defect in a maternal sample, and an assay to compare mitochondrial in a Down Syndrome fetus with mitochondria in normal patients, 2) a method for transplanting heterologous mitochondria into cells that have defective mitochondria and then using those cells for tissue generation, and 3) a neural stem cell that expresses UCP2 and UCP4 under the control of an inducible promoter and the method by which expression of UCP2 and UCP4 results in growth and differentiation of the stem cells into neural tissue.

Claims 1-12, 22-30 lack novelty under PCT Article 33(2) as being anticipated by Arbuzova et al (2002, BioEssays, 24:681-684). Arbuzova et al. teach in their review that work by Busciglio et al. (1995, Nature, 278:776-779) suggested that mitochondrial dysfunction is widespread in Down's Syndrome (page 682, first column first paragraph). Arbuzova et al. also teach that mitochondrial DNA (mtDNA) is almost entirely of maternal origin, as is the extra chromosome 21 in the vast majority of Down's Syndrome cases. It is also well-established that the number of mtDNA mutations increases with age in different cells, such as oocytes. Thus, it would be obvious to one in the art to obtain cells from the mother and determine if they contain mitochondrial defects.

Claims 13-21 and 31-38 lack industrial applicability as defined by PCT Article 33(4). Nothing in the art teaches that mitochondria can be extracted from one cell and put into another. This is a novel method and there is no way of knowing if it works (claims 13-21, 37, 38). The art teaches that little is known about the role of UCP2 and UCP4. While the Applicants teach that UCPs are expressed in neuronal stem cells, it is unclear how the expression of UCP2 and UCP4 has a role in growth and differentiation of neural stem cells.

Claims 13-21 and 31-38 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest that mitochondria can be transplanted from one cell to another (claims 13-21). The prior art also does not teach that UCP2 and/or UCP4 have a role in growth or differentiation of neural stem cells.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/14996

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 13-21 objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: neither the art nor the description provided by the Applicants teach how to transplant heterologous mitochondria from one cell to another.

Claims 31-36 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claism are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: neither the art nor the description provided by the Applicants teach that UCP2 and UCP4 predictably have a role in growth and differentiation of neural stem cells.